# Annual Reporting Form for SCEDDBO Projects and Cores

## Center Overview

Period covered by the report: 5/1/2007 – 4/30/2014
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda, Richard Auten, Sherman James, Pamela Maxson, Geeta Swamy, Allison Ashley-Koch, Alan Gelfand, Jerry Reiter
Project Period: Years 1-7

### Objectives of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO)

The central mission of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes was to determine how environmental, social, and host factors jointly contribute to health disparities. Specific aims of the Center were:

1. To develop and operate an interdisciplinary children's health research center with a focus on understanding how biological, physiological, environmental, and social aspects of vulnerability contribute to health disparities;
2. To enhance research in children's health at Duke by promoting research interactions among programs in biomedicine, pediatric and obstetric care, environmental health, and the social sciences and establishing an infrastructure to support and extend interdisciplinary research;
3. To develop new methodologies for incorporating innovative statistical analysis into children's environmental health research and policy practice, with a particular emphasis on spatial, genetic and proteomic analysis;
4. To serve as a technical and educational resource to the local community, region, the nation, and to international agencies in the area of children's health and health disparities; and,
5. To translate the results of the Center into direct interventions in clinical care and practice.

SCEDDBO leveraged and promoted active partnerships among the Nicholas School of the Environment at Duke University, the School of Natural Resources and Environment at the University of Michigan, the Duke University Medical Center, Trinity College of Arts and Sciences, and Duke's Children's Environmental Health Initiative, as well as the Durham County Health Department (DCHD), and Lincoln Community Health Center (LCHC), Durham's federally qualified health center. The Center brought together the expertise of obstetricians, pediatricians, genetic epidemiologists, spatial statisticians, environmental scientists, social epidemiologists, social psychologists, geographers, and community organizations. SCEDDBO capitalized on substantial ongoing commitments by Duke University to foster strong interdisciplinary research programs in environmental health sciences.

During the project period, SCEDDBO was characterized by significant synergies across center components. For example, our Community Assessment Project (CAP), conducted by the SCEDDBO COTC, assessed built environment variables for over 17,000 residential tax parcels in 2008 and for over 30,700 parcels in 2011, including the home addresses of over 65 percent of the 1800 participants in Project B's pregnancy cohort study and 4279 women from the Project A data architecture (with the latter number increasing as additional years of birth record data become available). Findings from analyses of these datasets led to the decision to incorporate a nest deprivation model in our animal studies, which originally focused on air pollution exposures

only. Over the course of the project period, we have published 80 papers resulting directly from the work of SCEDDBO.

Central to SCEDDBO's mission to determine how environmental, social, and host factors (see **Figure 1**) jointly contribute to health disparities was the development of an underlying, multi-sourced, detailed *data architecture*. During the project period, we constructed a large-scale, spatially referenced data warehouse, linking birth record data to social and environmental exposures data. Among women in our sample population, *exposure to air pollutants*, including PM2.5 and PM10, is associated with poor pregnancy outcomes (Chang et al., 2012; Gray et al., 2010;Vinikoor-Imler et al., 2012). We have helped define meaningful exposure metrics for air pollution and how to incorporate uncertainty in personal exposure estimates derived from monitoring station measurements (Gray et al., 2011). To do so, we constructed a stochastic simulator to directly make predictions of individual level exposure that we related to birth weight (Berrocal et al., 2011). Additional work on air pollution identified windows of vulnerability for pregnant women (Chang et al., 2012; Gray et al., 2010). We re-conceptualized the analysis for binary pregnancy outcomes (e.g., preterm birth) as a time-to-event analysis, enabling us to examine air pollution in a time-varying setting, where exposure is conditional on the length of the entire pregnancy or the third trimester (Chang et al., 2010). To achieve improved estimates of air pollution exposure, we constructed spatial downscalers, fusing monitoring station data with computer model output to better assess environmental exposure at point level spatial resolution (Berrocal et al., 2010a; Berrocal et al., 2010b; Berrocal et al., 2011).

Compared to non-Hispanic whites (NHW), non-Hispanic blacks (NHB) are more likely to live in neighborhoods characterized by poverty, elevated levels of environmental contaminants, and poor quality housing (Miranda et al., 2009). In related work on racial residential segregation (which is associated with higher environmental exposures), we observed a detrimental association between a spatial measure of neighborhood level racial residential segregation and pregnancy outcomes (Anthopolos et al., 2011). Racial residential segregation may impact health through the *built environment*. Using the Community Assessment Project data, we found that higher levels of housing damage, property disorder, tenure, and vacancy are associated with increased likelihood of preterm birth and low birth weight (Miranda, Messer, & Kroeger, 2012).

*Statistical methods development* has focused on outcome-exposure relationships. We emphasized joint modeling of related outcomes that can borrow strength from each other, such as birthweight and gestational age, which often helps with causal inference interpretation and illuminates subpopulations with differential risk for poor outcomes (Schwartz et al., 2010. See Figure XX). With binary outcomes (e.g., low birth weight and preterm birth) and normal outcomes, we have introduced additional borrowing of information with spatially correlated random effects (Neelon et al., 2012). Given the critical nature of health outcomes defined by distribution tails, such as low birth weight and preterm birth, in addition to the potential for differential covariate effects over the response distribution, we developed a new method to apply quantile regression in a spatial context (i.e., relaxing the assumption that observations in adjacent neighborhoods are independent). Applying this method, we observed differential effects of standard risk factors of birth weight, such as infant sex and birth order, along the birth weight response distribution.

We *recruited and retained* 1800+ women from Duke University Medical Center and Lincoln Community Health Center for our Healthy Pregnancy, Healthy Baby Study. Data on maternal and neonatal medical indicators, psychosocial health, and environmental exposures were obtained. We genotyped the cohort for 412 Single Nucleotide Polymorphisms (SNPs) in fifty-two genes related to human environmental contaminant clearance, infection and inflammation, maternal stress response, and other potential drivers of health disparities. To better identify subpopulations among NHB women in our sample, we generated the Illumina African American

Admixture Chip, based on 1509 selected SNPs with disparate frequencies in the Yoruban (African) and European (Caucasian) HapMap samples. As an example, we found that race-specific allelic frequencies in the vitamin D receptor (VDR) gene suggest its potential as a gene involved in health disparities (Swamy et al., 2011).

We found that women who live in neighborhoods with higher levels of housing damage, vacancy, and renter-occupied units are more likely to have poor scores on measures of psychosocial health, compared to women with residence in neighborhoods with lower levels of these attributes (Messer et al., 2012). Linking individual psychosocial health to the built environment, we then sought to understand the pathway between psychosocial health and pregnancy. Poor psychosocial health is associated with the likelihood of engaging in health behaviors known to be harmful to pregnancy, like smoking (Maxson & Miranda, 2011; Maxson et al., 2012; Miranda, Edwards, & Myers, 2011; Zhu et al., 2012). Among women for whom we measured levels of polybrominated diphenyl ethers (PBDE) flame retardants, our data suggest that PBDEs may be affecting thyroid regulation throughout pregnancy (Stapleton et al., 2011). In companion work, we observed that maternal behaviors and the presence of electronics were associated with higher levels of PBDEs in maternal cord blood samples (Buttke et al., 2012).

Additionally, we have characterized mercury and lead levels among women in our sample: socioeconomic status is positively related to mercury levels controlling for fish consumption, and lead levels were more likely to stem from remobilization from historical rather than current exposures (Miranda, Edwards, & Maxson, 2011; Miranda, Edwards, Swamy, et al., 2010).

The Healthy Pregnancy, Healthy Baby Study has motivated innovative methods development in the areas of handling *missing data* and developing *differential risk profiles*. While the cohort study had a high retention rate (92 percent), scattered missingness across the many collected variables resulted in a limited number of complete cases. We developed a non-parametric approach for multiple imputation via chained equations that uses sequential regression trees as the conditional models – an approach that we demonstrate can result in more plausible imputations and hence more reliable inferences (Burgette & Reiter, 2010). A second missing data problem that we encountered stemmed from a change in the laboratories used to measure environmental contaminants in maternal blood (Burgette & Reiter, 2012b). To overcome the statistical challenges associated with not having any measurements on both scales, we developed a multiple imputation approach based on rank preservation.

The amount of detailed information in the Healthy Pregnancy, Healthy Baby Study led us to concentrate on ways to distill variables into meaningful summaries in order to construct risk profiles. For example, through Bayesian growth mixture modeling, we differentiated classes of pregnant women according to their mean arterial blood pressure curves and joint probabilities of adverse birth outcomes (Neelon et al., 2011). Such classes may be more clinically relevant than looking at individual risk factors one at a time. With a similar goal but in a quantile regression setting, we developed ways to reduce high dimensional predictor spaces and identify latent factors underlying clusters of observed variables (Burgette et al., 2011; Burgette & Reiter, 2012a; Zhu et al., 2012).

We used *animal models* to more precisely assess the contributions of joint and sequential perinatal and postnatal environmental stressors on health outcomes. We exposed pregnant mice to a standardized industrial PM by tracheal instillation throughout pregnancy, followed by intermittent ozone exposure to their offspring. Maternal PM treatment induced inflammatory responses in fetal compartments and augmented the effects of ozone on airway hyper-reactivity, a model system for human asthma (Auten et al., 2009). We chose ozone as a criterion air pollutant to model human asthma since childhood exposure has been strongly associated with the development of asthma, and for the strong potential of early life ozone

exposure to have life-long health effects (Auten & Foster, 2011). In order to determine if traffic-related air pollutant exposure during pregnancy, already associated with the development of asthma and adverse pregnancy outcomes, could have similar 'priming' effects in offspring exposed to ozone, we exposed pregnant mice to inhaled diesel exhaust or to instilled diesel particles. Exposure to diesel via the ambient, physiological route (and by instillation) also caused fetal inflammatory responses (↑fetal lung and placenta pro-inflammatory cytokines) and worsened the effects of ozone on postnatal airway hyperreactivity. Notably, the combined pre-natal exposure of maternal diesel inhalation and postnatal ozone exposure of offspring impaired lung development, while single exposures did not. Furthermore, the effects on airway hyperreactivity persisted to adulthood after ceasing ozone exposure for four weeks, a completely novel finding, consistent with our hypothesized schema of synergies between exposures across the life span (Auten et al., 2012).

Our prenatal air pollution exposure models provoked fetal inflammation (lung, placenta), known to be linked with other adverse health outcomes such as impaired neurological development, so we began a collaboration with Staci Bilbo, (and eventually made her Co-PI on Project C) to examine long-term effects of combined perinatal pollutant exposure and other stressors known to be prevalent in impoverished communities (maternal stress, obesity, exposure to indoor antigens). We secured additional support from the Duke Institute for Brain Sciences to support these preliminary studies. We have since determined that pre-natal diesel exposure in mice during pregnancy, when combined with a high-fat diet provided to adult offspring, produces activated brain microglia, increases anxiety behavior, and impairs cognition (Bolton et al., 2012).

The synergy among the research projects was facilitated by the GIS and Statistical Analysis (GISSA) Core. The GISSA Core allowed for data analysis of the very large amount of data through the use of high-end GIS applications in combination with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, thus permitting multi-level analyses. Research Projects A and B both applied a Bayesian spatial hierarchical modeling approach to capture uncertainties in pregnancy outcomes and to elucidate the contributions of economic, sociocultural, and environmental stressors on health disparities in pregnancy outcomes. State-of-the-art GIS methods allowed for sophisticated spatial statistical analyses at highly resolved spatial scales.

The GISSA Core also provided the analysis of the biological response and genetic data generated in Research Projects B and C. The rich source of social, environmental, and host data in Project B, coupled with sophisticated statistical genetic approaches for identifying gene-gene and gene-environment interactions, provided the opportunity to make important discoveries of how these higher order interactions may be working together to promote or prevent adverse birth outcomes. By serving as a central clearinghouse for statistical analysis, the GISSA Core tracked outcomes in each project and used these discoveries to guide the analysis in each of the other projects.

The COTC provided key support by *developing community partnerships* and leading the community outreach and translation effort. COTC materials have been disseminated widely throughout the community, and the COTC has met often with community groups and local agencies. In collaboration with the nursing programs at Duke and UNC Schools of Nursing, COTC designed and regularly delivered a comprehensive curriculum to nursing students on environmental exposures and maternal and child health outcomes. The COTC also developed a partnership with nutritionists in the NC Supplemental Nutrition Program for Women, Infants, and Children (WIC), developing advisory materials on mercury fish consumption for Latino families. In addition, the COTC partnered with the GISSA Core to offer no-cost GIS training to public health personnel. COTC also collaborated with a variety of regional, state, and federal advisory

groups, SCEDDBO Director Marie Lynn Miranda served on the EPA's Children's Health Protections Advisory Committee (CHPAC).

**Partnerships**

A rich set of active relationships among community, campus, and organizational partners formed the basis for our center. First, we emphasized the connections among Duke, UNC, and U-M. Second, community partners and SCEDDBO investigators collaborated to improve environmental health in low-income areas throughout Durham County and across NC. These partnerships were and continue to be based on mutual interest in the effects of the environment on young children and pregnant women, as well as how environmental and social stressors interact to affect maternal and child health.

As a concrete example of our partnership approach, Durham Congregations, Associations, and Neighborhoods (Durham CAN) conducted a neighborhood audit that consisted of having volunteers take a block by block inventory of neighborhood problems, including broken or missing sidewalks, missing streetlights, roads in disrepair, litter, sewage and drainage problems, abandoned homes, and vacant/ overgrown lots. GISSA Core personnel converted the neighborhood audits into map-based visuals. Durham CAN used these maps in presentations to community groups, the Durham City Council, the Durham County Commissioners, and local government offices to negotiate improved conditions in target neighborhoods. In mapping the neighborhood audits for Durham CAN, we noted some clear problems with inter-coder reliability when comparing the audits across large sections of the city. We subsequently discussed joint work to improve the neighborhood audit. This collaborative effort formed the basis for the Community Assessment Project (see COTC).

During the project period, community partners and SCEDDBO investigators had multiple opportunities to explore mutual interests in designing projects that generate results that can be applied directly in the community. Our collective community-based experience convinced us that health disparities, particularly as they affect children, still represent the most important policy challenge in low income and minority communities. As we have jointly witnessed the disproportionate exposures to environmental contaminants, as well as the poor quality of the built environment and associated social stressors, we became convinced that real change in our communities requires an integrated understanding of environmental, social, and host factors.

**Publications listed under individual projects.**

## Administrative Core

Period covered by the report: 5/1/2007 – 4/30/2014
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda, Richard Auten, Sherman James, Pamela Maxson
Project Period: Years 1-7

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### Objectives of Core

The Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) was governed through an Administrative Core that includes an Executive Committee composed of the Director, the two Co-Directors, and the Project Manager; an Internal Steering Committee composed of members of the Executive Committee and the Directors of the Research Projects and the Facility and Community Outreach Cores, as well as a community member and the Director of the Durham County Health Department; and an External Advisory Committee composed of senior environmental health scientists, as well as community representatives, with expertise relevant to SCEDDBO, who provided informal consultation, as well as annual formal evaluation of Center research and outreach activities.

The specific aims of the Administrative Core are to:

a. Provide scientific direction and leadership;
b. Coordinate and foster interactions among research project and facility core investigators;
c. Provide administrative services for the Center;
d. Direct the Young Investigators program; and
e. Represent Duke's SCEDDBO to the university, the community, the NIH, other Children's Environmental Health Centers across the United States, and the policy and scientific community interested in children's environmental health more broadly.

In all activities, SCEDDBO emphasized the importance of diversity. The decision to focus on health disparities, the gender and racial diversity of Center leadership, the incorporation of natural, social and biomedical scientists, a commitment to community-based participatory research, and efforts to promote the careers of promising new investigators were all indicative of the importance that we place on fostering environments where all people can prosper.

### Progress Report/Summary of Accomplishments

*Leadership Changes.* Several leadership changes occurred over the project period. The SCEDDBO research group suffered a tremendous loss when our center co-director, Marcy Speer, died of cancer in August 2007. Richard Auten agreed to take on the role of center co-director. In addition, Jonathan Goodall moved from Duke to the University of South Carolina (USC). We requested that SCEDDBO be allowed to establish a sub-contract with USC, so that Goodall's work on water quality layers could continue uninterrupted. We also requested that Martha Keating be appointed director of the Community Outreach and Translation Core. All three of these requested changes were approved by the EPA. In 2010, Martha Keating relocated to the US EPA, at which time Pamela Maxson became director of the COTC. In addition, Dr. Evan Myers joined our Project A team in Year 4. Lastly, Dr. Sherman James resigned from his position on the executive team in preparation for his upcoming retirement.

*Quality Management Plan.* The Administrative Core developed and distributed a Quality Management Plan (QMP) to all SCEDDBO collaborators. These individuals signed the plan thereby agreeing that they had read the plan and pledging to abide by the policies laid out in the QMP. The Administrative Core kept a copy of these signed forms in its files.

*Young Investigators Program.* Over the period of the grant, Sherman James, Richard Auten and Marie Lynn Miranda mentored several individuals. Sherman James mentored Dr. Christina Gibson-Davis in the beginning of the project. Her research interests evolved substantially since SCEDDBO was awarded funding, and after two years, she asked to be relieved of her responsibilities on the SCEDDBO project. Drs. Miranda and Auten mentored Dr. Geeta Swamy. Over the course of the project, we built relationships with two new investigators, Dr. Heather Stapleton and Dr. Rebecca Fry, who were both mentored by Dr. Miranda.

*Project expenditures.* Expenditures over the project period matched projections in most areas. Spending on lab costs, particularly environmental and genetic analysis, was higher than anticipated, largely due to strong enrollment and sample capture. Project B expenditure were higher than expected, largely due to increased external costs such as the admixture chip and increased participant capture. We used discretionary dollars from the Administrative Core to cover some of these costs from Research Project B. Over the course of the project, some expenditures were lower due to personnel changes, enabling us to apply for a no-cost extension, which enabled us to continue our work. During the no-cost extension, most costs were associated with maintaining and expanding the animal models and continuing statistical and GIS analysis of the data. Dissemination costs were also incurred for conference presentation and publication costs.

*IRB Audit*. Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes was randomly selected by the Duke School of Medicine Compliance Office, Clinical Trials Quality Assurance Group for internal audit. This process took place from December 2007 through January 2008. The final report was received on January 30, 2008. The Administrative Core coordinated the interaction with the auditors. The overall assessment was extremely positive, and Project B staff received additional relevant feedback during the audit process.

*IRB Certification*. A centralized database on IRB and IACUC certification and continuing education requirements was maintained through the Administrative Core. Twice a year, Dr. Pamela Maxson, the QA Manager, verified that all researchers associated with SCEDDBO had completed their basic certification and continuing education requirements. Reminders were sent to investigators when they were due for additional training. In addition, Dr. Maxson was responsible for ensuring IRB and IACUC Protocols were renewed and updated as necessary. All of these documents were posted to the SCEDDBO internal website, and paper copies were centrally maintained by Dr. Maxson. This system was deemed successful in that all researchers on the SCEDDBO team maintained their certifications, allowing for uninterrupted access to SCEDDBO data, resources, and funds.

*Meetings*. The Executive Committee met monthly. We typically scheduled these meetings in advance of the Internal Steering Committee meetings in order to set the agenda for the larger group meetings. In addition, we held Science Advisory Committee (SAC) meetings at which staff associated with each center component developed a list of questions on which they especially sought the advice and guidance of the SAC. We held SCEDDBO retreats twice a year, focused on identifying and deepening synergies across the three core projects, as well as ways to continually improve our productivity.

*Website*. The Administrative Core provided material on SCEDDBO to the EPA for uploading to the EPA children's centers website. In addition, we updated our SCEDDBO website, linked off the website for the Children's Environmental Health Initiative (cehi.snre.umich.edu). We used our secure internal website that allowed for discussion boards, email communication, and document storage associated with the work of each of the SCEDDBO components.

*Dissemination*. SCEDDBO work was disseminated in a multitude of ways over the seven years of the project. Highlights are presented here; each project summary has a relevant list of publications and presentations.

Dr. Miranda brought her perspective on geospatial analysis and its usefulness in assessing and analyzing public health issues via her participation in the US Centers for Disease Control and Prevention's Geospatial Science and Healthy Communities Expert Panel, held in Atlanta, GA, in May 2008.

SCEDDBO offered a well-attended mini-symposium at the EPA in the Research Triangle Park in January 2009, designed to present EPA employees with a synopsis of the work that SCEDDBO does, emphasizing the environmental contributors to disparities in birth outcomes. Dr. Miranda represented the scientific mission of SCEDDBO as part of the USEPA's BOSC review of the agency's human health research program in January 2009. Specifically, Dr. Miranda co-authored and presented with Ms. Devon Payne Sturgess (USEPA) a poster regarding Long Term Goal 3 entitled "Differential Vulnerability to Environmental Contaminants and Adverse Outcomes during Early Childhood." This poster was well-received and SCEDDBO was commented on very favorably by the BOSC review panel in its written report.

Dr. Miranda represented the scientific mission of SCEDDBO as part of the GEI Exposure Biology Program in August, 2009. Specifically, Dr. Miranda presented a talk entitled "Combining Population Clinical, and Animal Models to Assess Exposure and Effects." Dr. Miranda also presented a talk at the USEPA's "Strengthening Environmental Justice Research and Decision-Making" conference. This talk was entitled, "Using GIS to Support EJ Results" and represented the broad work of the Children's Environmental Health Initiative, including work done under the auspices of SCEDDBO.

In addition, Dr. Miranda was the keynote speaker at our Nurses Conference, Environmental Considerations in Nursing Practice in May, 2010. She also spoke at the Environmental Health Summit in September, 2010. SCEDDBO also co-sponsored a symposium "The Social Context of Environmental Exposures in Children" in March, 2011. Speakers from Harvard, the United States Environmental Protection Agency, the National Institute of Child Health and Human Development, and Duke University discussed the role of the social context of environmental exposures in children. The symposium was well attended and garnered much positive feedback.

In 2012, Dr. Miranda gave the plenary address at ISEE in Columbia, South Carolina. Her talk, "Of Mice, Maps, and Moms: Air quality impacts on human health," discussed SCEDDBO's geospatial work on air pollution and its effects on pregnancy outcomes. In July 2013, she presented the keynote address, "It takes a village: Integrated methods for addressing environmental health disparities," at the NIEHS sponsored Environmental Health Disparities and Environmental Justice conference in RTP, North Carolina.

*Identification of training opportunities*. The Administrative Core worked with all of the other SCEDDBO components to identify key training opportunities for investigators and other research staff. Through this effort, we developed greater expertise in remotely sensed data, air pollution modeling, centering models of patient care, spatial statistics, and information science. These opportunities included both intensive short course and semester long coursework for several research staff, as well as travel to professional meetings for the graduate students and post-doctoral associates supported on the SCEDDBO grant. In addition, Dr. Alan Gelfand, Director of the GISSA Core, delivered a two-day intensive short course on spatial statistics that was widely attended by SCEDDBO investigators and research staff. We also offered training workshops through our Community Outreach and Translation Core, with administrative support provided through the Administrative Core.

*New Collaborations*. As part of our mission to both support the work of young investigators and advance the research mission of SCEDDBO, we began new collaborations with Dr. Staci Bilbo, Assistant Professor, Department of Psychology and Neuroscience, Duke University and Dr. Rebecca Fry, Associate Professor, Gillings Global School of Public Health, UNC. Our work with Dr. Bilbo focuses on new mouse models to explore the joint impact of environmental and social stressors on birth and developmental outcomes. Our work with Dr. Fry explores gene expression and epigenetic changes associated with *in utero* metals exposures, with a particular emphasis on cadmium. In addition, we established a CDC-funded collaboration with Dr. Heather Stapleton, Associate Professor, Nicholas School of the Environment, Duke University. This study leveraged our ongoing clinical obstetrics project to assess *in utero* exposures to brominated flame retardants, as well as the relationship between brominated flame retardant body burden and maternal thyroid function. Multiple papers were published on this collective work (Bolton et al., 2013; Edwards et al., in press; Stapleton et al., 2011; Sanders et al., 2013; Buttke et al., 2013).

*National Service.* Duke hosted the Children's Environmental Health Centers' monthly conference calls for several years, 2007-2013. SCEDDBO investigators also helped organize the October 2010 and 2013 Children's Centers conferences. In addition, Dr. Miranda served as a standing member of the Children's Health Protection Advisory Committee. Dr. Miranda also served as a chartered member of the NIH's Infectious Diseases, Reproductive Health, Asthma and Pulmonary Conditions (IRAP) Study Section. Multiple SCEDDBO investigators helped to review proposals for federal funding agencies, as well as review manuscripts for peer-reviewed journals.

**Project A: Mapping Disparities in Birth Outcomes**

Period covered by the report: 5/1/2007 – 4/30/2014
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Project Period: Years 1-7

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**Objectives of Research**
Project A utilized the conceptual framework of the "weathering hypothesis," which posits that chronic and persistent stressors lead to accelerated biological aging of women, which in turn accounts for adverse birth outcomes among certain subpopulations. The central objective was to determine whether and to what extent joint exposures to socioeconomic and environmental stressors contribute to racial and ethnic health disparities in fetal growth restriction.

Using a geographically-based nested study design moving from analysis of births for the entire State of North Carolina to six demographically and geographically distinct counties to a single health center and state-of-the-art Geographic Information Systems applications with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, the specific aims were to:

1. Spatially link detailed birth record, fetal death certificates, socioeconomic, environmental, tax assessor, community-based, and clinical obstetric data at highly resolved scales for the State of North Carolina from 1990-2003;
2. Refine the concept of fetal growth restriction by a) developing a joint distribution for birthweight and gestation using bivariate modeling for live births and fetal deaths – both separately and jointly, and b) defining it in terms of fetal and infant mortality, rather than percentile cut points; and
3. Determine whether and to what extent differential exposures to both environmental and social stressors help explain health disparities in fetal growth restriction among a) African-American women compared to Non-Hispanic white and Hispanic women, b) Older African-American women compared to younger African-American women, c) Hispanic women compared to Non-Hispanic white and African-American women, and d) Foreign born Hispanic women compared to US born Hispanic women.

This project evaluated a large number of factors in diverse populations, providing broad relevance for birth outcomes across time, space, and demography. Identifying social and environmental factors contributing to fetal growth restriction helped improve our understanding of disease etiology and explain the racial disparity in disease incidence.

## Summary

Central to SCEDDBO's mission to determine how environmental, social, and host factors jointly contribute to health disparities was the development of an underlying, multi-sourced, detailed *data architecture*. During the project period, we constructed a large-scale, spatially referenced data warehouse, linking birth record data to social and environmental exposures data. We have shown that among women in our sample population, *exposure to air pollutants*, including PM2.5 and PM10, and using proximity to roadways as a proxy variable, is associated with poor pregnancy outcomes, as measured by birth weight, preterm birth, and maternal medical

complications, controlling for maternal-level risk factors and neighborhood characteristics (Chang et al., 2012; Gray et al., 2010; Vinikoor-Imler et al., 2012; Gray et al., 2013; See Figure 2).

Our work has investigated how to define meaningful exposure metrics for air pollution in terms of the impact of geographic scale of aggregation and how to incorporate uncertainty in personal exposure estimates derived from monitoring station measurements (Gray et al., 2011). To do so, we constructed a stochastic simulator to directly make predictions of individual-level exposure that we related to birth weight (Berrocal et al., 2011). Additional work on air pollution has identified windows of vulnerability for expectant mothers (Chang et al, 2012; Gray et al., 2010). We re-conceptualized the analysis for binary pregnancy outcomes like preterm birth as a time-to-event analysis instead of simple logistic regression (Chang et al., 2012). With the goal of linking pregnancy outcomes to improved estimates of air pollution exposure, we have constructed spatial downscalers, which fuse monitoring station data with computer model output to better assess environmental exposure at point level spatial resolution (Berrocal et al., 2010a; Berrocal, et al., 2010b; Berrocal et al, 2011).

Compared to non-Hispanic whites (NHW), non-Hispanic blacks (NHB) are more likely to live in neighborhoods characterized by poverty, elevated levels of environmental contaminants, and poor quality housing (Miranda et al., 2009). In related work on racial residential segregation (which is associated with higher environmental exposures), we observed a detrimental association between a spatial measure of neighborhood level racial residential segregation and pregnancy outcomes (Anthopolos et al., 2011; See Figure 3). Racial residential segregation may impact health through the *built environment*. Using the Community Assessment Project data, we found that higher levels of housing damage, property disorder, tenure, and vacancy are associated with increased likelihood of preterm birth and low birth weight (Messer et al., 2012). Linking these two lines of research, we then showed in a formal mediation framework that poor quality built environment accounts for approximately 35% of the total effect of racial residential segregation on preterm birth (Anthopolos et al., 2014).

In our *statistical methods development*, we emphasized joint modeling of related outcomes that can borrow strength from each other, such as birthweight and gestational age, which will often help with causal inference interpretation and illuminate subpopulations with differential risk for adverse joint birth outcomes (Schwartz et al., 2010; See Figure 4.). For the case of binary outcomes (e.g., low birth weight and preterm birth) and normal outcomes, we have introduced additional borrowing of information at the contextual level with spatially correlated random effects (Neelon, Anthopolos, & Miranda, 2014; Neelon, Gelfand, & Miranda, 2014). Given the critical nature of health outcomes defined by distribution tails, such as low birth weight and preterm birth, in addition to the potential for differential covariate effects over the response distribution, we developed a new method to apply quantile regression in a spatial context (i.e., relaxing the assumption that observations in adjacent neighborhoods are independent). Applying this method, we observed differential effects of standard risk factors of birth weight, such as infant sex and birth order, along the birth weight response distribution (Lum & Gelfand, 2012).

In addition, we have completed work on the impact of maternal age and birth order on birth weight (Swamy et al., 2011), on modeling ordinal categorical data using Gaussian processes (Heaton et al, 2011), the etiology of racial disparities in maternal hypertensive disorders (Miranda et al., 2010), racial differences in seasonality patterns of poor pregnancy outcomes (Miranda et al., 2011), the advantages of spatial analysis in environmental health research (Miranda and Edwards, 2011), the relationship between early childhood lead exposure and later school performance and exceptionality designations (Miranda et al., 2007; Miranda et al., 2009; Miranda et al., 2010), on flexible Bayesian modeling techniques for functional and longitudinal

data (Montagna S. et al, 2012), on joint spatial modeling of areal multivariate categorical data (Tassone et al., 2010; see Figure 5), on optimal spatial designs for environmental health data (Environmetrics, Xia et al. 2006), on the association between the built environment and child BMI (Miranda et al., 2012), and on synthesizing categorical data sets from different sampling designs (Berrocal et al., 2013).

*Maternal Exposure to Air pollution*. Over the project period, we have done much work on air pollution exposure and pregnancy outcomes. A continuing goal was the linking of the detailed birth record data to USEPA $PM_{10}$, $PM_{2.5}$, and ozone monitoring data in order to study the impact of *maternal exposure to air pollution* on birth weight. To this end, in year 6 we were invited to write a review of air pollution effects on birth outcomes (Edwards et al., forthcoming). We were especially focused on incorporating refined exposure metrics to most effectively characterize meaningful exposures, as well as to capture any windows of vulnerability. Significant progress was made on the relationship between birth outcomes and exposure to particulate matter and ozone separately, and the current focus is determining how to characterize joint exposure to both particulate matter and ozone. A manuscript on this work appeared in the *Journal of Exposure Science and Environmental Epidemiology* (Gray et al., 2010). A critical issue in this work is addressing the misalignment between where monitoring stations are and where pregnant women live. Two approaches have been explored. One considers buffers of varying radii around monitoring sites to see how the exposure signal is affected by increasing distance from the site. The other attaches more uncertainty to the putative exposure as the distance from the monitoring site to the residence increases. Again, various exposure windows and metrics are considered. This work appeared in *Statistics and Medicine* (Gray et al, 2011). Time-to-event investigation of the effect of particulate matter and birth outcomes appeared in Chang et al. (2012a, 2012b).

As part of our larger efforts exploring the relationship of air pollution exposure and pregnancy outcomes, we sought to consider a relatively simple metric for assessing risk of exposure to air pollution, specifically traffic-related air pollution which includes particulate matter and diesel exhaust, both of which were investigated within Project C. We utilized the statewide GIS layer of street-geocoded 2005-2007 births to calculate the proximity of each geocoded birth to the nearest primary and secondary roadway. While controlling for all standard covariates, we incorporated measures of air pollution exposure as dichotomous variables indicating residence within 500, 250, 150, 100, or 50m of a primary or secondary roadway into models for birthweight, LBW, VLBW, PTB, VPTB, and any hypertensive disorder. Our findings indicate a significant dose-response relationship between proximity to a primary or secondary road and the adverse outcomes of PTB, VPTB and hypertension—for example, the probability of hypertension is increased by living within 500m of a primary or secondary roadway, with this probability being even higher at 250m, and still higher at each of 150, 100, and 50m (Miranda et al., 2013). In addition, much of our statistical development work, described below, used air pollution as the application.

*Nulliparous Women.* We explored the observed association between parity and risk of adverse birth outcomes (i.e., women having their first child are at increased risk of adverse outcomes compared to women who have already had at least one child). We linked births in the North Carolina Detailed Birth Record 1990-2007 with previous and subsequent births to the same mother using deterministic techniques that evaluated various combinations of maternal identifying variables to link births, including full name, maiden name, date and state of birth, parity, and date of last birth. We employed statistical and modeling-based analyses to estimate first birth outcome rate differences between nulliparas who did have a subsequent pregnancy versus those who did not. Among nulliparas that were not linked to a second birth, maternal-age-adjusted rates of multiple measures of adverse outcomes, including maternal medical

complications, were almost all statistically higher compared to rates for linked women. This work suggests that the observed differences in rates of adverse outcomes between nulliparas and multiparas are partly attributable to higher risk women not having a subsequent pregnancy (either by choice or due to fecundity differences). See Miranda, Edwards, and Myers, 2011.

*Racial Residential Segregation*. Our project on *racial residential segregation* enables quantification of racial exposure/isolation at finer spatial scales within SMSA's. Such a measure can be connected to measures of social and economic disadvantage at these scales to gain insight into how racial residential segregation has manifested itself across urban landscapes. In turn, this promises to reveal key insights into how to think about the spatial aspects of the social factors influencing health disparities. We are working to determine which facets of segregation best characterize the way community-level racial residential segregation acts to promote health disparities in birth outcomes. Although our initial efforts were statewide, we eventually decided that, given the significantly more detailed data available for Durham County, we would focus on this area to determine what variables are most important to characterizing racial residential segregation in terms of its health consequences (Anthopolos et al., 2011; Anthopolos et al., 2014; See Figure 6).

*Community Assessment Project/Built Environment.* Built environment data was collected under the Community Assessment Project (described under COTC) and preliminary analysis focused on spatial layers capturing four primary attributes of the built environment - housing damage, property disorder, tenure, and vacancy. Connection was made to pregnancy outcomes. Resultant work examining a bi-probit regression model as well as marginal logistic regressions has appeared (Miranda et al. 2012). Other work connecting the built environment with adverse birth outcomes appears in Miranda, Messer, & Kroeger, 2012. Other manuscripts are described in Project B.

*Seasonality.* We have examined the relationship between seasonality and pregnancy outcomes. Our initial aspatial models indicated that the effect of season was most apparent among non-Hispanic white women (Miranda, Anthopolos, & Edwards, 2011). We utilized spatial models to better understand what factors of season of conception or birth are influencing pregnancy outcomes.

*Racial Disparities in Maternal Hypertensive Disorders.* We analyzed data from North Carolina to determine how the pattern of maternal hypertensive disorders differs among non-Hispanic white, non-Hispanic black, and Hispanic women across the range of maternal ages. In addition we explored whether rates of poor birth outcomes, including low birth-weight and preterm birth, among hypertensive women differed by race (Miranda et al., 2010; Neelon et al. 2011, Vinikoor-Imler, 2012)

*Developmental Outcomes.* Having linked the North Carolina statewide detailed birth record and educational record databases, we examined the impact of pregnancy-related events and exposures on neurodevelopmental outcomes in early childhood. Two manuscripts have been published. The first, published in *JAMA Pediatrics*, (See Gregory et al. 2013), investigates whether induction and/or augmentation during labor may be associated with autism diagnosis in children in grades 3-8. In this work, we used logistic regression modeling for rare events data to first establish an association between labor induction/augmentation and autism diagnosis and then examine whether the association is robust to controlling for successive sets of potential confounders related to maternal demographics, maternal health conditions, and events of labor and delivery, as recorded in the detailed birth record. The second is in *Pediatric and Perinatal Epidemiology*, examining the joint effect of birth outcomes and maternal prenatal smoking on educational test scores in reading and math (Anthopolos et al. 2013). This study finds that maternal prenatal smoking may interact with birth outcomes on reading and mathematics test

scores, particularly among non-Hispanic white children. Additionally, improvements in birth outcomes, even within the clinically normal range, may be associated with improved academic performance.

*Environmental Contributions to Disparities in Pregnancy Outcomes.* We published an invited review article on social and environmental contributors to disparities in birth outcomes based on both national and North Carolina data, as a way of compiling the many literatures we have accessed throughout our work on Project A. The manuscript, published in *Epidemiologic Reviews*, reviews research on how environmental exposures affect pregnancy outcomes and how these exposures may be embedded within a context of significant social and host factor stress.

*Statistical Methods Development.* Our work was highly focused on statistical methods development, particularly in the areas of leveraging Bayesian hierarchical spatial modeling and developing multivariate modeling approaches to examining correlated outcomes.

Out of efforts to develop new spatial methodologies for addressing health disparities, we did additional methodological work on *disaggregated spatial modeling for areal unit categorical data.* This work used innovative statistical methodology that extends spatial disease mapping techniques to model subgroups within areal units using a spatially smoothed, multilevel loglinear model. This work appeared in the *Journal of the Royal Statistical Society, Series C* (Tassone, et al., 2010). An attractive feature of this methodology for public health applications is the possibility to elucidate health disparities across space, across subgroups, and space-subgroup interactions.

Another completed manuscript builds *joint models for birthweight and gestational age* using bivariate normal mixtures. Such joint modeling adjusts for maternal risk factors and provides mixture analysis of the residuals to help illuminate further subpopulations with differential risk for adverse joint birth outcomes. Modeling of the mixture components is done through gestational age and then birthweight given gestational age. Joint modeling eliminates potential causal inference concerns. A paper has appeared in *Statistics in Medicine* (Schwartz et al., 2011). Follow-on work extended this effort to incorporate spatial structure, introducing spatial random effects in the regression modeling for both outcomes (Neelon et al. 2012).

We also examined *quantile regression methodology* in explaining the effect of exposure on pregnancy outcomes. Rather than explaining mean birthweight as in customary regression models, we explaini quantiles for birthweight. For instance, it would be of interest to explain the $10^{th}$ percentile of birthweight since this is the threshold for declaring small for gestational age. Our work demonstrated that risk factors and environmental exposure affect different quantiles differently. See Lum and Gelfand 2012.

In addition, we developed a flexible Bayesian spatial discrete-time survival model to estimate the effect of environmental exposure on the risk of preterm birth. We view gestational age as time-to-event data where each pregnancy enters the risk set at a pre-specified time (e.g. the 32nd week). The pregnancy is then followed until either: (1) a birth occurs before the 37th week (preterm); or (2) it reaches the 37th week and a full-term birth is expected. As preliminary analysis, the methodology was applied to a dataset of geo-coded births in North Carolina from 2002. We estimated the risk of preterm birth associated with short-term exposure to fine particulate matter using air quality metrics derived from the EPA's Statistically Fused Air Pollution Database. We also conducted a simulation study and compared the proposed approach to the standard case-control and time series design. See Chang et al., 2012 and Chang et al., 2013.

Related work has studied the use of a $PM_{2.5}$ exposure simulator to explain birthweight. In a published paper, a template is developed for using an *environmental dose simulator* to connect ambient exposure to personal exposure. Then, using various exposure metrics, calculated form these personal exposures, which are clinically plausible over the course of a pregnancy, linkage is built to adverse birth outcomes (Berrocal et al., 2011).

Another component of our work focused on building *spatial downscalers*. Such modeling strategies enable the fusion of monitoring station data with computer model output to better assess environmental exposure at point level spatial resolution. Such downscalers can be dynamic, enabling the tracking of exposure through time. With improved estimation of local exposure, we can better examine linkage between exposure and adverse birth outcomes. Three papers on this methodology have been published. The first, for the univariate case, appeared in the Journal of Agricultural, Biological and Environmental Statistics (Berrocal et al, 2010). The second considers the bivariate problem, looking at downscaling two exposures (ozone and PM2.5), borrowing strength in the joint modeling (Berrocal et al. 2010). The third focused on measurement error associated with downscaling. Such error is attributable both to misalignment between monitoring sites and model grids as well as to effects of neighboring grids on local monitoring site levels (Berrocal et al., 2012).

Significant progress was made on the relationships between air pollution exposures, socioeconomic status, and birth outcomes. We extended our methodological work with *spatial downscalers* to conduct an applied analysis on racial and socioeconomic disparities in exposure to air pollution across the State of North Carolina (see Gray et al. 2010). While previous studies of the environmental justice dimensions of air pollution limit analysis of populations living near air quality monitoring stations, we used space-time downscaling methods that we previously developed to output predictive surfaces of ozone ($O_3$) and particulate matter < 2.5 μm in aerodynamic diameter ($PM_{2.5}$) at the census-tract level covering all of North Carolina. This analysis sought to provide a better understanding of the environmental justice dimension of air pollution exposure across the entire North Carolina population. Moreover, in additional work (see Gray et al., 2014), we linked the downscaled output to the detailed birth record in order to examine the joint effects of socioeconomic status and air pollution on birth outcomes, using the highly resolved estimated pollution exposures. The downscaled output allowed us to estimate the association between air pollution exposure and birth outcomes for times and locations where exposure data were otherwise unavailable.

We also continued building joint models in order to examine correlated outcomes. Joint modeling eliminates potential causal inference concerns (Schwartz et al., 2010). In work under preparation, we examine the association between features of the built environment with the bivariate outcome of preterm birth and low birthweight (MacLehose et al, in preparation). Additionally, we have developed multivariate spatial modeling to accommodate correlated continuous outcomes (Neelon et al, 2014.). This latter work incorporates correlation not only between jointly modeled outcomes but also among mothers living in nearby neighborhood units.

We furthered methodological work on expected performance accruing to *synthesizing categorical datasets*, with the objective of enhancing inference deals with a collection of datasets of varying sizes that are all relevant to a particular scientific question, but which include different subsets of the relevant variables, with some overlap (see Berrocal et al., 2012). We synthesized cross-classified categorical datasets drawn from a common population where many of the sets are incomplete (i.e., one or more of the classification variables is unobserved), but at least one is completely observed. The method is expected to reduce uncertainty about the cell probabilities in the associated multi-way contingency table.

We have synthesized our hypotheses concerning the adverse effects of *racial residential segregation* on the one hand, and *poor quality built environment* on poor birth outcomes on the other. Using advanced mediation models as the basis for our analytical approach, we examined whether poor quality built environment acts as a mediator in the relationship between racial residential segregation and preterm birth. This work developed a novel method to maintain an additive scale in estimating natural direct and indirect effects from non-linear models (e.g., logistic regression). Additivity is required for interpreting the proportion of the total effect (i.e., the effect of the exposure, racial residential segregation, on the outcome) explained by the mediator (i.e., the poor quality built environment) in a causal framework. In addition, we developed a summary poor built environment index to avoid violating assumptions of no unmeasured confounding in the mediation model (Anthopolos et al, 2014).

**Supplemental Keywords:** Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling, racial residential segregation, built environment, birth outcomes

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**2010**

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**Research Project B:** ***Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes***

Period covered by the report: 5/1/2007 – 4/30/2014
EPA Agreement Number: RD83329301-0
Investigators: Redford Williams (PI), Allison Ashley-Koch, Christina Gibson-Davis, Pamela Maxson, Marie Lynn Miranda, Jerome Reiter, Geeta K. Swamy,
Project Period: Years 1-7

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**Objectives of Research**

The central objective of the Healthy Pregnancy, Healthy Baby Study was to determine how the interaction of environmental, social, and host factors contributes to disparities in birth outcomes between African-American and white women in the American South. There were four specific aims:

1. Conduct a cohort study of pregnant women in Durham, NC designed to correlate birth weight, gestation, and birth weight x gestation with environmental, social, and host factors;
2. Develop community-level measures of environmental and social factors by inventorying neighborhood quality and the built environment in partnership with local community groups;
3. Create a comprehensive data architecture, spatially resolved at the tax parcel level, of environmental, social, and host factors affecting pregnant women by linking data from the cohort study and neighborhood assessments with additional environmental and socioeconomic data; and
4. Determine whether and to what extent differential exposures explain health disparities in birth outcomes by applying innovative spatial and genetic statistical methods to:
    a. Identify environmental, social, and host factors that cluster to predict birth outcomes in the entire sample,
    b. Determine whether these clusters are more or less present in African-American versus white populations and quantify the proportion of health disparities explained by differences in cluster frequency, and
    c. Identify environmental, social, and host factors that cluster to predict birth outcomes within the African-American and white sub-samples and compare these clusters across racial groups.

We successfully recruited 1889 women into our prospective cohort study, Healthy Pregnancy, Healthy Baby. Women were recruited from Duke University Medical Center (DUMC) and Lincoln Community Health Center. Demographic data indicate that we were highly successful recruiting women most at risk for adverse pregnancy outcomes, particularly low-income, low educational attainment, and non-Hispanic black women.

The following information was collected from participants in the Healthy Pregnancy, Healthy Baby Study:

- Psychosocial measures: CES-D, perceived stress, self-efficacy, interpersonal support, paternal support, perceived racism, perceived community standing, pregnancy intention, John Henryism Active Coping Scale, NEO Five Factor Inventory of personality.
- Environmental exposure survey measures: short survey on fish consumption, smoking pattern and exposure to second-hand smoke, and drinking water source.

- Maternal and neonatal medical record abstraction: detailed pre-pregnancy medical and social history, antepartum complications, birth outcomes, and neonatal complications.
- Blood samples for genetic and environmental analysis to assess candidate genes related to environmental contaminant (nicotine, cotinine, cadmium, lead, mercury, arsenic, and manganese) metabolism, inflammation, vascular dysfunction, and stress response.
- Cord blood and placental samples are currently being stored for future genetic analysis and evaluation of activity at the maternal-fetal interface.

We were also highly successful in collection of participant-level data as well as biological samples, with greater than 90% attainment of maternal blood sample for genetic and environmental analyses. Collection of cord blood and placental samples, which began in June 2007, has also been successful with approximately 960 delivery samples collected.

All maternal data have been georeferenced (i.e., linked to the physical address of the mother) using Geographic Information System (GIS) software. The Healthy Pregnancy/Healthy Baby Study also included two in-depth neighborhood assessments designed to capture both built environment and community-level social stressors and community resources. In order to increase the participant capture rate (first assessment: 40%), we expanded our second assessment area, successfully capturing approximately 70% of the participants. The cohort study and neighborhood assessment data are spatially linked to extensive environmental and demographic data at a highly resolved spatial scale.

We genotyped the cohort for 412 Single Nucleotide Polymorphisms (SNPs) in fifty-two genes related to human environmental contaminant clearance (heavy metals and environmental tobacco smoke), infection and inflammation (cytokines, chemokines, and bacterial pathogen recognition), maternal stress response (serotonin), and other pathways that have been implicated as potential drivers of health disparities (vascular responsivity). To better identify subpopulations among NHB women in our sample, we generated the Illumina African American Admixture Chip, based on 1509 selected SNPs with disparate frequencies in the Yoruban (African) and European (Caucasian) HapMap samples. For the purpose of addressing population stratification, we used clustering algorithms on the Illumina data to identify sub-populations within our NHB women and found that indeed some stratification does exist. Thus, we used the genome-wide percentage of European admixture as a continuous covariate in our candidate gene analyses.

**Genetic Analysis**

The ***Vitamin D receptor gene (VDR)*** has a wide variety of functions, including calcium homeostasis and modulating circulating levels. Subtle genetic variation has also been linked to adverse conditions including diabetes, cancer, renal disease, and autoimmune disorders. In multivariable regression modeling, we found a significant association between the VDR variant (rs731236, a coding, synonymous SNP) and preterm birth ($p=0.04$) for non-Hispanic black (NHB) women in our study population. The odds of having an infant born preterm were 2.9 times higher for women with the CC genotype at this marker compared with women with the TT genotype ($p=0.04$) and were 3.8 times higher for women with the CC genotype compared with women with the CT genotype ($p=0.01$). This same association did not hold true among the non-Hispanic white (NHW) women. Furthermore, in addition to 6 other SNPs within the VDR gene, rs731236 was also associated with infant birthweight among NHB but not NHW women (Swamy et al., 2011)

The nitric oxide (NO) pathway is critical for managing oxidative damage in a variety of tissues. Reduced levels of endothelial nitric oxide synthase (NOS3) have been previously linked to pre-eclampsia, a maternal complication associated with preterm birth. But also pertinent to this

project is that specific polymorphisms within the inducible nitric oxide synthase (NOS2A) gene have been associated with protection against malaria, thus there may be population specific selective forces leading to differential allele frequencies for the polymorphisms in these genes. For these reasons, we hypothesized that polymorphisms within the NOS genes may differentially affect risk for preterm birth among African American mothers in our cohort. We examined 57 SNPs in the three nitric oxide synthase genes (NOS1, NOS2A and NOS3) for association with risk for preterm birth in our cohort. We identified 10 SNPs in NOS1 which were nominally associated with risk for preterm birth in our non-Hispanic white (NHW) subset of mothers. Only 1 SNP in NOS2A was nominally associated with preterm birth in our non-Hispanic black (NHB) subset of mothers. Thus, we did observe differential association with these genes and preterm birth as a function of maternal race. However, we were surprised that the effects that we observed were stronger for the NHW subset rather than the NHB subset.

We have also examined polymorphisms in the **G-protein coupled receptor kinase 5** (GRK-5) gene. GRK5 is associated with a pharmacogenomic interaction among African Americans in the setting of cardiovascular disease and response to β-adrenergic receptor (βAR) blockade, which is standard therapy for cardiac failure and ischemia. Because of the association with cardiovascular disease, we hypothesized that GRK-5 genetic variation was associated with hypertensive disorders in pregnancy. We defined hypertensive disorders as chronic hypertension (CHTN=BP>140/90 before 20 wks), preeclampsia (BP>140/90 and proteinuria), and CHTN + superimposed preeclampsia (CHTN with new onset or worsening proteinuria). Haplotype tagging single nucleotide polymorphisms (SNPs) were genotyped for GRK-5 via Taqman assays. Logistic regression was used to examine the relationship between maternal genotype and each hypertensive disorder among the NHB women, adjusting for age, education, insurance, tobacco use, and pre-pregnancy BMI. CHTN was included as a covariate in the model for preeclampsia. In our NHB data set, 125 out of 587 participants (21%) were diagnosed with preeclampsia. Of the 17 SNPs examined, 3 were nominally associated with preeclampsia. For the most significant association with rs10886445 (global p=0.0009), the odds of preeclampsia for NHB women with the CC genotype were 0.28 times that for NHB women with the TT genotype (CI: 0.1429, 0.552). For those NHB women with the CT genotype, the odds of developing preeclampsia were 0.33 times that for NHB women with the TT genotype (CI: 0.1682, 0.656). In addition, rs12416565 (global p=0.003) and rs11198925 (global p=0.02) were also nominally associated. For CHTN, only one marker (rs2420620, global p=0.02) demonstrated nominal association. Similarly, for CHTN+preeclampsia, only one marker (rs10510055, global p=0.02) demonstrated nominal association. Based on these results, we concluded that the GRK-5 gene may play a role in hypertensive disorders of pregnancy, particularly the development of preeclampsia.

In our NHB women, we have examined G*E between genes in the inflammatory pathway and ETS as they relate to infant birthweight and identified several nominal associations, the most significant being rs2069771 in the interleukin-2 gene with cadmium exposure (global p=0.005) and rs9005 in the interleukin 1 receptor antagonist with cadmium exposure (global p=0.006). In addition, also among the NHB women, we have identified G*E interactions between the n-acetyltransferase genes and cadmium exposure predicting maternal preeclampsia and infant outcomes. In particular, rs8190845 in NAT1 interacted with cadmium exposure to predict occurrence of preeclampsia in the mother (global p=0.009). Additionally, rs17126345 , also in NAT1, interacted with cotinine exposure to predict the occurrence of preterm birth as defined as delivery prior to 37 weeks gestation (global p=0.006).

The inflammatory response influences risk for adverse birth outcomes such as low birthweight. Variability in maternal inflammatory response may be exacerbated by exposure to air pollution during pregnancy. We examined how variation in maternal inflammatory genes interacts with

air pollution to affect infant birthweight (BWT) in 673 non-Hispanic black (NHB) women participating in the Healthy Pregnancy, Healthy Baby Study. Maternal residential address at enrollment was georeferenced, and the distance to the nearest major roadway was calculated as a proxy for traffic-related air pollution exposure. 105 haplotype tagging SNPs were genotyped in 20 candidate genes on maternal DNA samples. Linear regression was used to examine the relationship between SNPs and infant BWT, adjusting for infant sex, maternal age, parity, education, insurance, and smoking use. We also examined interactions between SNPs and roadway proximity. Consistent with previous reports, genetic variation in the inflammatory response provided evidence for main effects on infant BWT among NHB women in our study. We provide the first evidence that some of these genes interact with air pollution exposure to influence infant BWT.

**Environmental Sampling**

Using the maternal environmental blood samples collected on all participants in Project B, we characterized maternal exposures to toxics.

*Lead*. In addition to documenting the blood lead burdens among a cohort of pregnant women in Durham County, NC, we have been able to characterize current maternal exposures to lead by linking each participant to the tax parcel at which they resided during their pregnancy. We found that both year built and modeled lead exposure risk at participant's residence during pregnancy were not predictive of maternal blood lead levels. Taken in combination with results showing that maternal blood levels increased with age, these findings indicate that maternal blood lead levels are much more likely the result of lead remobilization from historic exposures as opposed to contemporaneous exposures (Miranda et al., 2010).

*Mercury.* Using self-reported fish consumption and maternal blood samples, we examined correlates of mercury levels during pregnancy. Higher income and education were associated with greater fish consumption, as well as higher levels of mercury when controlling for fish consumption (Miranda, Edwards, & Maxson, 2011). Our work with mercury led to our collaboration with Women, Infants, and Children (WIC) in North Carolina to craft culturally appropriate messages for Latina women who consume fish caught in North Carolina waters. This project is described under the COTC.

*Cadmium*. Cadmium is prevalent in the environment and understudied as a developmental toxicant. We conducted an analysis of maternal cadmium exposure and leukocyte DNA methylation patterns in 17 mother-newborn pairs. A methylated cytosine-guanine (CpG) island recovery assay was used to assess over 4.6 million sites spanning 16,421 CpG islands. Exposure to cadmium and cotinine was classified for each mother-newborn pair according to maternal blood levels. Comparative methylation analysis was performed to identify genes with differential methylation levels. DNA motifs that were overrepresented among the differentially methylated genes were identified. Subsets of genes were identified that showed altered DNA methylation levels in fetal DNA associated with exposure to cadmium (n=61), cotinine (n=366), or both (n=30). In maternal DNA, subsets of cadmium-associated (n=92) and cotinine-associated (n=134) genes were identified. While the gene sets were largely distinct between mothers and newborns, functional similarities at the biological pathway level were identified including transcriptional regulation and apoptosis. Furthermore, conserved DNA motifs with sequence similarity to specific transcription factor binding sites were identified within the CpG islands of the gene sets. This pilot investigation provides evidence for distinct patterns of DNA methylation alterations in fetal and maternal DNA associated with exposure to cadmium. The genes with differential methylation share common motifs at the sequence level suggesting that structural commonalities in DNA sequence may affect environmentally-related DNA methylation status (Sanders et al., 2013). A paper describing risk factors for elevated levels of cadmium

during pregnancy is forthcoming (Edwards, et al., forthcoming), and a paper linking cadmium levels with pregnancy outcome has been submitted (Johnson, et al., in submission).

*Polybrominated Diphenyl Ether (PBDE).* Our clinical obstetrics work led to a fruitful collaboration with Dr. Heather Stapleton, a leading expert in PBDE research. This work examined PBDE levels in pregnant women and the association with thyroid hormones (Stapleton et al., 2011) and pregnancy outcomes (Miranda, et al., in submission). In Stapleton et al. (2011), we found that BDEs 47, 99, and 100 were significantly and positively associated with free and total thyroxine levels and with total triiodothyronine levels above the normal range. The more recent work (by Miranda et al.) shows that while certain maternal PBDE levels are negatively associated with infant head circumference, the relationship does not appear to be mediated by thyroid hormone levels.

*Additional Projects*

*Residential mobility***.** With our access to the North Carolina Detailed Birth Record (DBR) in Project A, we have been able to link participants in Project B with their birth certificate data. Using maternal and infant identifying information, including name, place, and date of birth, we have been able to link 991 (99.9%) of participants who completed the study and had a live birth by December 31, 2008 and 59 (76.6%) of participants who were lost-to-follow-up but with an expected delivery date on or before December 31, 2008. This linkage allowed us to determine who is moving during pregnancy (by comparing the address at enrollment and the DBR address at delivery) and the nature of those moves, including the quality of the new location compared to the previous location (and thus changes in environment or exposure).

*Proximity to Roadways.* In parallel to the Project A work with road proximity metrics, we geocoded Project B participants to the tax parcel level and then calculated the distance to the nearest roadways. We extended the road proximity work in Project A by incorporating the rich set of variables available in Project B, including analysis looking at how psychosocial health and gene-by-environment interactions may influence the impact of traffic-related air pollution on birth outcomes (Miranda et al., 2013).

*Community Assessment Project/Built Environment*. The Community Assessment Project (CAP) assessed built environment variables at two times (2008 and 2011) for over 17,000 and 34,000 tax parcels, respectively, including the home addresses of over 70% of the participants in the Healthy Pregnancy, Healthy Baby Study (SCEDDBO Project B). Seven scales (housing damage, property disorder, security measures, tenure, vacancy, violent crime, and nuisances) have been constructed at five levels of geography (census block, primary adjacency neighborhood, census block group, census tract and city-defined neighborhoods). Analyses have assessed the relationship between the built environment and maternal psychosocial status (Messer et al., 2012) and pregnancy outcomes (Miranda et al., 2012).

*Psychosocial Indicators.* Analyses have been completed on psychosocial influences on birth outcomes. The relationships among pregnancy intention, psychosocial health, and pregnancy outcomes have been examined, with a paper published (Maxson et al. 2011). In addition, we have examined pregnancy intention, behavioral choice, and environmental exposures. The influences of psychosocial health and smoking status have been studied, with a resulting publication (Maxson et al. 2012). In order to reduce the number of psychosocial variables, cluster analysis has been performed, resulting in three distinct clusters of women. Cluster analysis on the personality indices was also performed. A paper examining the relationship between the built environment as measured through the Community Assessment Project and women's psychosocial health was published (Messer et al., 2012). We will continue analysis with a focus on the relationships among psychosocial health, risk behaviors, chemical and non-chemical stressors, and pregnancy outcomes.

*Maternal Medical Complications.* Fetal health is not only individually determined, but is also influenced by maternal health and well-being. We continue our emphasis on maternal outcomes. In particular, we have focused on hypertensive disorders during pregnancy. We have identified factors that affect maternal blood pressure during pregnancy. In order to make use of all blood pressure readings collected across the pregnancy, we considered a variety of statistical approaches, including latent trajectory and sparse functional data models (Neelon et al., 2011).

*Statistical Methods Development.* We developed new statistical methodologies designed to improve analysis of the Project B data, as well as to advance statistical analysis more broadly. A paper detailing statistical methodology developed in year 5 for accounting for mid-study changes in measurement scales won the Youden award for the best paper in interlaboratory testing methods this past year (Burgette & Reiter. 2012). These methods were needed because the Project B investigators switched laboratories for measuring blood levels of heavy metals midway through data collection in order to take advantage of finer measurement scales. Exploratory analysis indicated that the distributions of levels for several exposures were markedly different across the labs, so that analyses based on a simple concatenation of the two labs' data would be biased. Using the second lab scale as the standard, so that effectively measurements before the lab switch are treated as missing, we developed general purpose methodology for imputing plausible values of the missing exposure measurements. The methods are based on assumptions about the relative ranks of measurements in the two scales, e.g., a measurement in the $10^{th}$ percentile in one scale should be at the $10^{th}$ percentile in the other scale. We implemented this methodology on the Project B data to provide the investigative team with improved data.

In addition, we developed and implemented methods for finding important predictors in quantile regression when there are a very large number of covariates. These methods adapted the lasso and elastic net penalties for quantile regression. We applied the methods on a mid-study sample of women to uncover a previously unreported interaction: women who smoke and who have high blood lead levels tend to have babies with lower birth weights (Burgette et al. 2012).

We developed and implemented methods for using factor analysis models in the context of quantile regression. The investigative team believed that many of the predictors can be grouped into underlying factors. For example, the Project B data contain several variables that measure maternal stress, and arguably we should connect birth outcomes to the underlying factor of stress rather than its individual indicators. As another example, the data contain several imperfect indicators of smoking status, and we wanted to connect birth outcomes to the underyling factor of true smoking status. We implemented the model on a mid-study sample of women from Project B, and we found that the smoking factor was a strong predictor of low birth weight. An article on this research was accepted for publication in *Biometrics* (Burgette & Reiter, 2012).

We also developed a Bayesian growth mixture model to jointly examine the associations between longitudinal blood pressure measurements, preterm birth (PTB), and low birthweight (LBW). The model partitions women into distinct classes characterized by a mean arterial pressure (MAP) curve and joint probabilities of PTB and LBW. Each class contains a unique mixed effects model for MAP with class-specific regression coefficients and random effect covariances. To account for the high correlation between PTB and LBW, we introduced a bivariate probit model within each class to capture residual within-class dependence between PTB and LBW. The model permits the association between PTB and LBW to vary by class, so that for some classes, PTB and LBW may be positively correlated, while for others, they may be uncorrelated or negatively correlated. We also allowed maternal covariates to influence the

class probabilities via a multinomial logit model. For posterior computation, we proposed an efficient Markov chain Monte Carlo algorithm that combines full-conditional Gibbs and Metropolis steps. We applied our model to a sample of 1027 women enrolled in the Healthy Pregnancy, Healthy Baby Study. A manuscript was published at *Statistics in Medicine* (Neelon et al. 2011).

We developed new ways of handling missing data in large epidemiological studies in which interaction effects are suspected. The main approach is to adapt regression trees to perform multiple imputation. This approach was used to handle the missing data in Project B. This methodology has the potential to be utilized in a wide range of settings, including outside of epidemiological contexts. An article describing this work has been published in the *American Journal of Epidemiology* (Burgette et al., 2010).

The team also examined approaches to performing Bayesian analysis after multiple imputation is used for missing data. This work was motivated by the use of the tree methodology for multiple imputation, because we are estimating Bayesian models with the completed datasets. This research was published in *The American Statistician* (Zhou et al., 2010).

Finally, the team developed an approach for assessing sensitivity to unmeasured confounding when using principal stratification. This work was motivated by the presence of several intermediate variables in the prospective study of Project B, e.g., hypertension as an intermediate variable for gestation age. At this point, this work is at a theoretical stage; we have not yet applied it on Project B data. A manuscript on the theory has been published in *Statistics in Medicine* (Schwartz et al., 2012).

*Statistical Methods Development for Genetics*. We also developed statistical methods for the genetic data. The first statistical innovation involving the genetic data is the adverse sub-population regression (ASPR) for multi-variate outcomes with high dimensional predictors. The ASPR is a two component latent class model, with the dominant component corresponding to (presumed) healthy individuals and the risk of falling in the minority component characterized via a logistic regression. The logistic regression model is designed to accommodate high-dimensional predictors, as occur in studies with a large number of gene by environment interactions, through use of a flexible nonparametric multiple shrinkage approach. The Gibbs sampler is developed for posterior computation. The method was evaluated with the Project B data and has been published in *Statistics in Medicine* (Zhu et al., 2012).

The second innovation involving the genetic data was motivated by our analysis of the admixture data. The current genetic analysis tool that is most widely used (ANCESTRYMAP) is very limited in that it only allows consideration of qualitative, not quantitative, outcomes and does not allow for the incorporation of covariates. Thus, we have extended this method in our project (Zhu et al., 2012).

One of the statistical innovations that we have been working on is the improvement of methodologies for admixture mapping. To that end, we developed a generalized admixture mapping (GLEAM) approach, a flexible and powerful regression method for both quantitative and qualitative traits, which is able to test for association between the trait and local ancestries in multiple loci simultaneously and adjust for covariates. The new method is based on the generalized linear model and utilizes a quadratic normal moment prior to incorporate admixture prior information. Through simulation, we demonstrated that GLEAM achieves lower type I error rate and higher power than existing methods both for qualitative traits and more significantly for quantitative traits. See Zhu et al., 2013.

**Supplemental Keywords:** Pregnancy, preterm birth, low birth weight, racial disparity, African American, environmental stressors, gene-environment interactions, psychosocial stressors, genes, single nucleotide polymorphisms

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**Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health**

Period covered by the report: 5/1/2007 – 4/30/2014
EPA Agreement Number: RD83329301-0
Investigators: Richard Auten (PI), W. Michael Foster
Project Period: Years 1-7

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**Objectives of Research: Specific Aims**

1. To determine whether maternal exposure to airborne particulates (PM) and/or ozone (1st hit) restricts fetal growth and/or postnatal growth, and impairs lung development/function in newborn mice;
2. To determine whether PM and/or ozone exposure 're-programs' maternal inflammatory responses;
3. To determine whether postnatal (2nd hit) ozone exposure further impairs postnatal somatic and lung development/function following maternal PM and/or ozone exposures;
4. To determine whether genetic or developmental susceptibility to airway hyperreactivity exacerbates maternal and/or postnatal exposure effects on postnatal somatic and lung development/function.

**Progress Report/Summary of Accomplishments (in chronological order)**

Significant progress was made in Project C. We determined that postnatal ozone (1 ppm x 3h/d, 3 d/week x 4 weeks) significantly impairs postnatal weight gain in C56BL/6 mice. *Air pollutant exposure at a vulnerable window of postnatal development impairs growth*. We also saw that postnatal ozone increases nebulized methacholine induced airway hyperreactivity (AHR) in C57BL/6 mice measured at 4 weeks but not 3 weeks. *Ozone induced AHR is developmentally regulated*.

We have that prenatal instillation of particulate matter (St. Louis particle, NIST#1648) twice weekly in time mated pregnant mice augments postnatal ozone-induced AHR in mice, measured at 4 weeks postnatal. *Prenatal air pollutant exposure reprograms postnatal air pollutant responses that result in AHR* (Auten et al., *Am J Resp Crit Care Med* 2009).

In studies in collaboration with M. Ian Gilmour, EPA , we exposed time-mated C56BL/6 pregnant mice to internal combustion engine diesel exhaust (0.5, 1, & 2 mg/m$^3$ x 6h/d, 5d/week, from gestation day 6-17) v. air control. Pups delivered to exposed dams were exposed postnatally to ozone as described above. Prenatal diesel exposure dose-dependently impaired lung compliance and pressure-volume loop hysteresis v. air or prenatal air postnatal ozone controls. There were parallel effects on nebulized methacholine challenge induced AHR. *Prenatal ambient exposures to diesel particulates at doses relevant to human environmental exposure worsened postnatal ozone-induced lung function and AHR*.

We published a manuscript that reported the effect of prenatal diesel particulate pulmonary exposure on postnatal ozone induced airway hyperreactivity (Auten et al., *Am J Resp Cell Mol Biol*., 2012). The report showed dose-dependent effects of particulate matter inhalation on maternal inflammatory responses; synergistic effects of prenatal diesel exposure and postnatal ozone exposure on lung inflammatory cytokine responses, synergistic effects of prenatal diesel and postnatal ozone on postnatal airway hyperresponsiveness to inhaled methacholine challenge.

Because increasing evidence links non-chemical stressor effects on mothers and offspring to both AHR and cognitive development, we sought to determine if other stressors that would be typical co-exposures in human experience would potentially exacerbate effects of air pollution exposure. In impoverished environments in the US, this would include resource/housing deprivation and uncertainty, as well as poor diet. We therefore sought collaboration with investigators with expertise in behavioral/cognitive development and neuroinflammation, since that mechanism was likely common to the inflammatory mechanisms that underpin pollution effects on AHR.

We developed a mouse model of nest-restriction during pregnancy that had no effects on maternal licking and grooming in the first postnatal week, but which apparently unmasked adverse effects of diesel inhalation during pregnancy. Combined prenatal diesel aspiration and pre-natal nest restriction of pregnant mice induced increased anxiety in offspring of both sexes and impaired cognition in male offspring. This sexually dimorphic response was parallel to changes in brain IL-1β and IL-10. Findings were reported in Bolton et al., *Environmental Health Perspectives* (2013) 121(9):1075-82. Only the combination of diesel inhalation and resource deprivation produced this finding. This suggests the importance of studying exposures in combination. However, our preliminary studies showed that these combined stressors did not affect AHR.

Because obesity is common to both childhood asthma and poverty, we conducted studies to determine if post-natal high fat diet could also worsen or unmask prenatal diesel effects on behavior and cognition. We exposed time-mated mice to spontaneous diesel exhaust in collaboration with Ian Gilmour US EPA. Offspring were randomly assigned to normal or high fat diet after weaning. The offspring that had combined prenatal exposure to inhaled diesel (dams) and post-natal high fat diet showed increased brain microglial activation, but only males demonstrated decreased spontaneous activity and increased anxiety behavior. Prenatal air pollution appeared to program offspring for increased susceptibility to diet-induced weight gain. These findings were reported in Bolton *et al*. (2012) *FASEB J*.

**Supplemental Keywords:** Airway hyperreactivity, diesel exhaust particles, air pollution, lung function, epigenetic, innate immunity, Nqo1, neuroinflammation, maternal stress

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Miranda, ML, Edwards, SE, Chang, HH, Auten, RL. 2013. "Proximity to Roadways and Pregnancy Outcomes." *J. Exp Science Env Epi,* 23: 32-38. PMID: 22805991.

**Presentations**

**2008**

Auten, RL. "Fetal and Neonatal Programming of Child and Adult Lung Diseases." Pediatric Grand Rounds, Duke University Medical Center. August 5, 2008.

Auten, RL. "Pre-natal inhaled pollutant exposure augments postnatal ozone induced airway hyperresponsiveness" Visiting Pulmonary Scholar Program. October 8, 2008. Friday Center, University of North Carolina at Chapel Hill, Chapel Hill, NC.

**2009**

Auten, RL, Mason, SN, Potts, EN, Gilmour, MI, Foster, WM. "Maternal Diesel Exhaust Particle (DEP) Inhalation Worsens Postnatal Ozone induced Airway Hyperreactivity (AHR) in Mice" Pediatric Academic Societies. 2009. Baltimore MD.

Potts, EN, Auten, RL, Mason, SN, Foster, WM. "Pulmonary susceptibility of neonatal mice to ozone modulated by NQ01." American Thoracic Society International Conference. 2009. San Diego CA.

**2010**

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Auten, RL. U.S. EPA "Combining Air Pollution Exposures with Resource Deprivation: Lessons from Mouse Models." Protecting Children's Health for a Lifetime: Environmental Health Research Meets Clinical Practice. October 18, 2010.

**2011**

Huff, NC, Bolton, JL, Mistry, RS, Smith, SH, Auten, RL, Bilbo, SD. "Effects of Combined Early-life Social and Environmental Stressors on Affect Cognition and Brain Cytokine Expression." Society for Neuroscience. November 12, 2011. Washington, DC.

**2012**

Auten, RL. Seminar “Air Pollution Exposure in Pregnancy Effects on Respiratory Function in Offspring: Innate Immunity as Gateway.” Duke University Integrated Toxicology Environmental Health Program. February 17, 2012.

Auten, RL. “Embracing Complexity: Animal Models of Environmental Health.” EPA/NIEHS 2012 Webinar Series: Protecting Children’s Health for a Lifetime.

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Bolton, JL., Huff, NC., Smith, SH., Mistry, RS., Potts-Kant, EN., Auten, RL., Bilbo, SD. “Maternal Stress Exacerbates the Effects of Prenatal Air Pollution Exposure on Brain & Lung Cytokine Expression and Cognitive and Affective Outcomes in Offspring in a Sex-Specific Manner” Society for Neuroscience. October 13-17, 2012. New Orleans, LA.

Bolton, JL., Mason, SN., Potts, EN., Gilmour, MI,, Foster, WM., Auten, RL., Bilbo, SD. “Sexually dimorphic placental responses to maternal air pollutant exposure: the root of sex differences in behavioral and metabolic outcomes of adult offspring?” Organization for the Study of Sex Differences. June 7-9, 2012. Baltimore, MD.

## Community Outreach and Translation Core

Period covered by the report: 5/1/2007 – 4/30/2014
EPA Agreement Number: RD83329301-0
Investigators: Martha H. Keating; Pamela Maxson (PI), Marie Lynn Miranda
Project Period: Years 1-7

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### Objectives of Research

The central objective of the Community Outreach and Translation Core (COTC) was to create, implement, and assess strategies to translate and apply the findings of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) into relevant information for women of childbearing age, families, community groups, policy makers, and health care professionals. The COTC conducted environmental health outreach and education directed at low income and minority women and their children; enhanced the capacity of disadvantaged communities to understand threats posed by environmental contaminants; and provided a bridge between campus research, communities and policy makers. The specific aims of the COTC were:

1. Support the community-based neighborhood assessment being undertaken as part of Research Projects A and B;
2. Partner with nursing programs at Duke-affiliated hospitals to develop and present curricula to nursing students on environmental exposures and maternal and child health outcomes;
3. Develop culturally-appropriate advisory materials on environmental contaminants for low-income expectant or nursing mothers with low English proficiency;
4. Deliver training to local health department personnel focused on environmental factors related to maternal health and pregnancy outcomes;
5. Participate in regional, state and federal policy dialogues to provide decision makers with policy-relevant science-based information concerning environmental exposures and health disparities related to maternal and child health and well-being; and
6. Increase awareness of maternal health and health disparities by facilitating bi-directional exchanges between Center investigators, community members, public health advocacy groups, and policy makers.

### Progress Report/Summary of Accomplishments

The Community Outreach and Translation Core (COTC) was an integral component of SCEDDBO, translating and disseminating research findings to the scientific and neighborhood communities. Over the project period, the COTC developed a wide and diverse network of collaborators among federal, state and local agencies, universities, and community groups. Activities with these diverse partners cover a broad spectrum of children's environmental health issues, ranging from birth outcomes to lead poisoning prevention, environmental exposures, and obesity. Importantly, the COTC responded with detailed information to numerous requests from private citizens about a variety of environmental health concerns. Topics have ranged from lead and mercury exposure to electromagnetic fields, chloramines, and exposure to rubber crumblets. These requests were received through both the CEHI toll-free number and via the CEHI website.

We describe here four major contributions, which reflect Specific Aims 1-4, of the COTC during the project period. Specific Aims 5 and 6 were a part of the COTC's daily mission. The end of the project has not lessened the commitment of the COTC to continue to serve the community. The COTC remains dedicated to fostering environments where all children can prosper.

**Community Assessment Project.** In Durham, there is continued city-wide concern over quality of life issues including neighborhood safety, housing quality, and poverty. During the summer of 2008, a team of COTC-trained assessors conducted an on-foot, curb-side assessment of approximately 17,000 tax parcels in Durham, North Carolina, evaluating the built environment on 57 variables using handheld Global Positioning System (GPS) devices. The exercise was repeated again in the summer of 2011 over a larger geographic area that included roughly 30,700 tax parcels. Built environment data were combined with Durham crime data and tax assessor data. The two phases also captured 40% and 70%, respectively, of the physical addresses for participants in the Project B cohort, providing a detailed characterization of the local neighborhood environment for a significant subset of participants. In collaboration with the GISSA Core, CAP data were summarized into seven Neighborhood Health Indices. These indices have been linked to outcomes from Projects A and B. Our collaboration with community partners at all stages of the tool development, data collection, and dissemination of results provides a model for engaging the community in an active research program. The COTC has disseminated the CAP results to multiple audiences (community members, public health professionals, and government officials) through publication of a descriptive report, creation of web-based resources, and in-person presentations. COTC personnel attended community meetings across the network of community-based organizations to discuss and display the results of the CAP and work with interested stakeholders on how to utilize the CAP results in their community development efforts. The COTC will continue to disseminate the CAP results to multiple audiences (community members, public health professionals, and government officials) through publication of a descriptive report, creation of web-based resources, and in-person presentations. The need extends past the project end date.

**Building Capacity in Health Professionals.** COTC investigators partnered with nursing programs to develop and present curricula to nursing students on environmental exposures and maternal and child health. A comprehensive project was designed to develop environmental health curricula for nursing students, nursing faculty, and practicing nurses. Supplemental funding from EPA's Environmental Education Grant Program has enabled collaborations with the Ecology Center in Ann Arbor, MI to produce this curriculum. The resources developed during this project provide: (1) an organized synthesis of current information; (2) foundational knowledge for nursing school faculty; and (3) subject modules on environmental health concepts that can be incorporated into existing nursing curricula.

The COTC partnered with the GISSA Core to offer no-cost, hands-on training on environmental health issues, including the built environment, to public health professionals throughout North Carolina. Four all-day sessions were attended by 65 participants representing 18 NC counties, 18 different program areas of state government, 7 non-profit organizations, and Durham city personnel. This course has broad ranging public health applications including policy guidance, community outreach and education, and program planning. The training was accredited for continuing education credits for Registered Sanitarians (the professional certification common to county health department personnel).

The COTC also partnered with the UNC School of Nursing and Healthcare without Harm to co-sponsor an environmental health symposium for practicing nurses. The symposium, Environmental Considerations in Nursing Practice attracted nationally-recognized speakers and an audience of 60 practicing nurses. The event was also accredited for Continuing Nursing

Education credits. COTC staff participated in all aspects of the planning and execution of this conference. SCEDDBO Director Marie Lynn Miranda presented the keynote address.

**Culturally-Appropriate Advisory Materials on Environmental Contaminants**. The COTC created and delivered culturally-appropriate methylmercury-contaminated fish consumption advisory information for low income expectant or nursing mothers with low English proficiency. COTC collaborated with the NC Women and Infant Children (WIC) Program to design, test, and deliver appropriate risk communication materials relating to NC fish consumption advisories for methylmercury and federal advisories for a number of commercial fish species. The Latino population is at risk of methylmercury exposure from fish consumption, but may not be effectively reached through traditional fish advisory communication methods. Together with staff from the NC Nutrition Services Branch (within the Department of Health and Human Services), we created an outreach model for communicating complicated environmental health information to pregnant or early postpartum Latina women. The intended audience was the nearly 17,000 Latina women who participate in the Supplemental Nutrition Program for Women, Infants, and Children (WIC) in NC. Of all of the Latino babies born in NC in 2005, 53% were born to mothers who participate in the WIC Program. In particular, we were interested in designing and testing culturally/linguistically appropriate messages and message delivery formats for fish consumption advisory information. The COTC established a number of dissemination efforts to distribute the mercury fish consumption fish advisory materials that were developed for Latino families (see Figure 8). Because the materials were distributed to families primarily by nutritionists in the North Carolina Supplemental Nutrition Program for Women, Infants, and Children (WIC), considerable effort was expended to reach this audience. A series of webinars, accredited for continuing education credits for Registered Dieticians, were held for all WIC staff in North Carolina. The webinars were attended by 109 participants representing 66 out of 88 (80%) of the WIC clinics in North Carolina. This work was adopted as part of the standard messaging from WIC counselors to WIC enrollees after the COTC personnel trained the counselors. This project also serves as a prototype for identifying best practices for communicating complex environmental health messages in culturally sensitive context.

**Strong Partnerships**. COTC staff collaborated with a variety of regional, state, and federal advisory groups including the American Lung Association Advisory Group, the Durham County Health Department Community Health Assessment Working Group, and the Obesity and Chronic Disease Committee of the Partnership for a Healthy Durham. In addition, SCEDDBO Director Marie Lynn Miranda was appointed to serve on the EPA's Children's Health Protection Advisory Committee (CHPAC). The CHPAC is a federal advisory committee established in 1998 to provide independent advice to the EPA Administrator on regulations, research, and communications issues relevant to children's environmental health.

SCEDDBO investigators and the COTC PI, in particular, have established longstanding relationships with multiple community and organizational partners throughout NC and nationally. These include the NC Department of Environment and Natural Resources, Children’s Environmental Health Branch; the NC Department of Health and Human Services, Occupational and Environmental Epidemiology Branch; the NC Center for Geographic Information and Analysis; state and local health departments throughout NC, as well as in other states (AR, CA, CO, IA, ID, IN, KS, LA, MA, ME, MI, MN, MS, MT, NC, NE, NH, NM, NY, PA, SC, SD, TX, UT, VT, WI); the Southeast Pediatric Environmental Health Specialty Unit; and a host of community-based organizations and public health advocacy groups. SCEDDBO investigators have also established connections with physicians, pharmacists, religious leaders, day care centers, and community centers. Furthermore, SCEDDBO investigators have developed relationships with agency officials from the CDC, HUD, the NIH, and the USEPA.

For all seven years, COTC investigators mentored students from Duke University and the University of Michigan in the “Break the Cycle” project sponsored by the Region 4 of the U.S. EPA, Emory University, the Institute of Disadvantage and Disability, and the Southeast Pediatric Environmental Health Specialty Unit. The selected students presented environmental health data from SCEDDBO projects (Ouyang, 2011; Dadabhoy, et al., 2012; Modlin & Maxson, 2011; Gruber & Maxson, 2012; Henderson & Maxson, 2009; Koehrn & Keating, 2009; Martz et al., 2013; Henry et al., 2013). The conference was held in Atlanta, GA, every spring. In May 2011, Dr. Pamela Maxson gave the keynote address at the conference (Maxson, 2012).

**Supplemental Keywords:**

Risk communication, outreach, translation, participatory research, built environment

**Publications**

Dadabhoy, F., Maxson, P., and Auten, R. 2012. “Perinatal Exposure to Air Pollutants has Adverse Effects on Behavioral Outcomes in Mice.” *International Journal of Disability in Human Development* 11(4).

Gruber, A. and Maxson, P. 2012. “Disparities in Psychosocial Health and the Built Environment during Pregnancy.” *International Journal of Disability in Human Development* 11(4).

Henderson, K., Maxson, P. 2009. “Obesity Intervention Strategies and the Built Environment in a Low-Income, Minority Population.” *International Journal of Child and Adolescent Health*.

Henry, H., Anthopolos, R., & Maxson, P. 2013. “Traffic Related Air Pollution and Pediatric Asthma.” *International Journal of Disability in Human Development.*

Koehrn, K., Keating, M. 2009. “The Regulation of Agricultural Pesticides in North Carolina: Implications for Farm Workers and Their Families.” *International Journal of Child and Adolescent Health*.

Kroeger G.L., Messer L., Edwards S.E., and Miranda M.L. 2012. “A Novel Tool for Assessing and Summarizing the Built Environment.” *International Journal of Health Geographics,*11(46). PMID: 23075269.

Martz, M., Anthopolos, R., Geller, M., and Maxson, P. 2013. “Pediatric Obesity and Food Access in Durham, NC.” International Journal of Child Health and Human Development, 7(3).

Modlin, E. and Maxson, P. 2010. “Breaking the Cycle of Maternal Depression: An initiative to Improve Children’s Environmental Health.” *International Journal of Child Health and Human Development*, 3: 405-411.

Maxson, P. 2012. “Together We Can Break the Cycle.” *International Journal of Disability in Human Development* 11(4).

Miranda, ML, Keating, MH, Edwards, S. 2008. “Environmental Justice Implications of Reduced Reporting Requirements for the Toxics Release Inventory Burden Reduction Rule.” *Environ. Sci. Technol.* 42(15): 5407-14.

Ouyang, R. 2011. “The Relationship between the Built Environment and Birthweight.” Rev Environ Health 2011;26(3):181–186.

**Presentations**

**2007**

Coley, RY, Davis, J, Collins, A, Ingram, A, Marin, K, Miranda, ML. "Developing a Tool for Conducting Assessments of the Built Environment." American Public Health Association. November 2007. Washington, DC.

Keating, MH. "Fish Choices: Balancing Benefits and Risk." Annual North Carolina WIC Program Conference. September 2007. Raleigh, NC.

**2008**

Henderson, K., Maxson, P. "Obesity Intervention Strategies and the Built Environment in a Low-Income, Minority Population." Paper Presentation, Break the Cycle III Conference. May 2008. Atlanta, GA.

Keating, M. "Southern Center on Environmentally Driven Disparities in Birth Outcomes." North Carolina Preconception Health Task Force, Women and Obesity Work Group. January 2008. Chapel Hill, NC.

Koehrn, K., Keating, M. "The Regulation of Agricultural Pesticides in North Carolina: Implications for Farm Workers and Their Families." Paper Presentation. Break the Cycle III Conference. May 2008. Atlanta, GA.

Miranda, ML. "Effective Interventions for Preventing Lead Poisoning." USEPA Beyond Translation Workshop. October 2008. Research Triangle Park, NC.

SCEDDBO investigators. "Southern Center on Environmentally-Driven Disparities in Birth Outcomes." Research Symposium presented at the USEPA. January 2009. Research Triangle Park, NC.

**2009**

Keating, MH., Richardson, L., Connaughton-Espino, T. "Hook, Line, and Sinker: Developing, Delivering, and Testing Fish Advisory Messages for Latinas." 2009 National Environmental Public Health Conference. October 28, 2009. Atlanta, GA.

Keating, MH, Richardson, L., Connaughton-Espino, T., Miranda, ML. "Delivering Complex Environmental Messages in Cultural Context."137$^{th}$ Annual APHA Meeting. November 7-11, 2009. Philadelphia, PA.

Kroeger, GL, Miranda, ML., Davis, J. "Community Assessment: Understanding the Built Environment with a Neighborhood Health Context." 137$^{th}$ Annual APHA Meeting. November 7-11, 2009. Philadelphia, PA.

Modlin, E., Maxson, P. "Breaking the Cycle of Maternal Depression: An Initiative to Improve Children's Environmental Health." Break The Cycle. September, 2009. Atlanta, GA.

**2010**

Kroeger, GL, "The CEHI Community Assessment Project: A Tool for Linking the Built Environment with Key Health Outcomes." Strengthening Environmental Justice Research and Decision Making: A Symposium on the Science of Disproportionate Environmental Health Impacts. March 17, 2010. Washington, DC.

Miranda, ML. "Environment Matters: An Overview of Public Health and the Environment." Environmental Health Nursing Conference. May 2010. Chapel Hill, NC.

Ouyang, R., Keating, M., Maxson, PJ. "There Goes the Neighborhood: The Relationship between the Built Environment and Birth Weight in Central Durham, NC." Break the Cycle. May 2010. Atlanta, GA.

**2011**

Dadabhoy, F., Maxson, P., and Auten, R. “Perinatal Exposure to Air Pollutants has Adverse Effects on Behavioral Outcomes in Mice.” Break the Cycle Conference. May 2011. Emory University, Atlanta, GA.

Gruber, A. and Maxson, P.“Disparities in Psychosocial Health and the Built Environment during Pregnancy.” Break the Cycle Conference. May 2011. Emory University, Atlanta, GA.

Maxson, P. "Breaking the Cycle – a Multilayer Approach." Invited Keynote, Break the Cycle Conference. May 2011. Emory University, Atlanta, GA.

Maxson, P. "Disparities in Environmental Exposures." Invited talk. Addressing Prenatal Environmental Health Effects on Mother and Fetus, A Workshop Hosted by Southeast Pediatric Environmental Health Specialty Unit and Institute for the Study of Disadvantage and Disability. May 2011. Centers for Disease Control, Atlanta, GA.

**2012**

Henry, H., and Maxson, P. “Traffic-related Air Pollution and Pediatric Asthma in Durham County, North Carolina.” Break the Cycle Conference. May 2012. Emory University, Atlanta, GA.

**2013**

Martz, M. and Maxson, P. “Pediatric Obesity and Food Access in Durham, NC.” Break the Cycle Conference. April 2013. Emory University, Atlanta, GA.

## Geographic Information System and Statistical Analysis Core

Period covered by the report: 5/1/2007 – 4/30/2014
EPA Agreement Number: RD83329301-0
Investigators: Alan Gelfand (PI), Allison Ashley-Koch, Jonathan Goodall, Marie Lynn Miranda, Jerome Reiter
Project Period: Years1-7

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### Objectives of Research

The overall objective of the GIS and Statistical Analysis Core was to **support spatial and quantitative analysis needs of the Center research projects, as well as the Community Outreach and Translation Core.** Our specific aims included:

1. Providing support for the development of environmental and social data layers needed to implement data analyses required for the research projects and the Community Outreach and Translation Core;
2. Providing statistical analysis, advice, and consulting on the broad range of statistical issues that arise in conjunction with the research projects, with a particular emphasis on data reduction methods and modeling spatial and spatio-temporal data within a Bayesian framework; and,
3. Providing analysis for the unique needs of genetic data arising from the clinical and animal studies of the center.

This support core facilitated the development of innovative quantitative methodology for children's environmental health research associated with the projects and cores. Equally important, it enhanced substantive collaboration between statisticians and scientists involved in the research projects yielding improved analyses of research core data, as well as novel statistical modeling.

### Progress Report/Summary of Accomplishments

Over the project period, the GISSA Core built and maintained a spatially and temporally linked data architecture for maternal and child health outcomes from the prenatal period to early childhood. The central objective was to track mothers and offspring in their residential environments at varying time slices. While capitalizing on the extensive data warehouse that we had assembled since the Center's inception, we continued to integrate data layers into the architecture such as metrics from the EPA's Air Quality System, National-Scale Air Toxics Assessment, fused air pollution data combining modeled and monitored data, and in-house constructed road proximity measures, in addition to the most recently available years of North Carolina statewide administrative data on births, educational outcomes, and blood lead levels. Based on linking methods described in previous reporting periods, the unique individual-level identifying record enables connections across multiple administrative databases on births, blood lead surveillance, deaths, and educational outcomes. These datasets can each be examined separately and in various combinations according to the master linking file.

With the completion of participant recruitment in Project B in August 2011, GISSA staff focused on data quality control/quality assurance, along with finalizing the project analysis dataset and planning related studies with the participants. All of the participants have been integrated into a geographic information system with information on environmental exposures, factors of the built environment, and standard demographic data.

In addition to data acquisition, management, and georeferencing, the GISSA Core provided innovative statistical support to each of the Projects. In Project A, the GISSA Core developed

spatial models to better characterize associations between birth outcomes and environmental exposures, including air pollution and the built environment. In Project B, the GISSA Core supported multiple imputation efforts to construct finalized imputed datasets based on the full study population.

The GIS team street geocoded all residential addresses in the 1990-2012 DBR data for the State of North Carolina, with the exception of 2010 births due to transitions in the birth record.. Street geocoding, which allows us to link births to Census data resolved at the block level, have been completed for 80% of 1990-2009 birth records, with success rates increasing over time up to 82% by 1999. Success rates increased significantly as the years progressed, with 2000-2009 geocoded at 86% and 2011-2012 geocoded at 95%.

The DBR is compiled from questionnaires obtained at the time of birth certificate filing and includes elements essential to our proposed analyses. Available variables include, *inter alia*: maternal residence and state and country of birth; marital status; maternal and paternal race, Hispanic ethnicity, and education; alcohol and tobacco use; plurality; parity; maternal complications; congenital anomalies; whether an infant death certificate was filed; and infant birth weight and gestational age. All 22 years of data have been integrated and standardized to facilitate data linkages and statistical analysis.

We developed methods for linking the North Carolina DBR data with other clinical and administrative datasets. These methods rely on the individually-identifying variables provided in the DBR, including full name and date of birth of both infant and mother. We first applied this methodology to link DBR data with participant data from Project B, matching participants who delivered between 2005 and 2009 to their corresponding record in the DBR. This linkage allowed us to examine how accurately the administrative dataset (DBR) captures key information, as well as undertake analysis of residential mobility during pregnancy. Using the 1990-2007 DBR, we linked births occurring to the same mother. This linkage allowed us to examine internatal spacing and birth outcomes across pregnancies, and by further combining this data with the DBR-linked Project B data, we were able to capture the participants' subsequent pregnancy outcomes. In addition, we used this method to link the DBR data with an administrative datasets of educational outcomes at the individual child level, which allowed us to examine how disparities in birth outcomes may have long-term implications for child development.

We expanded the environmental data layers available for use through the SCEDDBO data warehouse to include spatial data on road intensity, criteria air pollutants from the USEPA's AQS system, water quality, environmental releases documented in the Toxics Release Inventory, and housing quality.

We genotyped 1600 blood samples from pregnant women for 412 Single Nucleotide Polymorphisms (SNPs) in fifty-two genes, primarily involved in either metabolism of heavy metals or immune response. In addition, we generated the Illumina African American Admixture Chip on 1016 NHB women.

The GISSA Core provided innovative statistical support to each of the Projects. For example, in Project A (references included under Project A), the GISSA Core provided statistical methods development to obtain unbiased estimates of the effect of air pollution exposure on birth outcomes (Chang et al. 2012) and address measurement issues in aggregated estimates of ambient exposure to air pollution (Berrocal et al. 2012; Gray et al. 2011; Berrocal et al. 2011). The GISSA Core marked a second publication on multiple imputation in Project B (references included under Project B). This work extended previously developed imputation methods (Burgette et al. 2012) to handle inconsistent laboratory measurements (Burgette et al 2012).

In support of both Projects A and B, the GISSA Core developed quantile regression techniques to examine the effect of risk factors of interest at varying quantiles along the outcome distribution, rather than limiting analyses to mean effects. As a continuation of the Center's work on joint outcome modeling (Lum & Gelfand, 2012; Burgette et al. 2011; Burgette et al. 2012), the GISSA Core also developed multivariate (Neelon et al. 2011) modeling techniques to better understand individual and shared risk factors of related health outcomes, in addition to capturing geographic variation in disease risk through spatial methods.

Despite the project period ending, we will continue to develop and expand the geospatial data warehouse that supports analysis among various projects. The GIS team will continue to identify additional environmental layers to integrate into our data architecture. With the construction of the spatio-temporal data architecture, we will continue to conduct analyses that leverage the spatial and longitudinal nature of the data, focusing on the quantile and multivariate approaches already developed by our team. We will continue analyses on approximately 1,600 Project B participants with complete pregnancy data, genetic results, and environmental results. Analyses will look at the joint impact of environmental, social, and host factors on birth outcomes, especially as they differ by and within race. Identification of such co-exposures could lead to development and implementation of strategies to prevent adverse birth outcomes, ultimately decreasing or eliminating the racial disparity.

**Supplemental Keywords:**

Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling